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10/812,849	03/30/2004	Todd Zankel	30610/40037	3684

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1649	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/812,849	ZANKEL ET AL.	
	Examiner	Art Unit	
	Daniel Kolker	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *3/5/07, 4/20/07*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-19,21,22 and 58-62* is/are pending in the application.

4a) Of the above claim(s) *22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-19,21 and 58-62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *17-19,21-22,58-62* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/5/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Sequence alignment (2 pgs)*.

DETAILED ACTION

1. The remarks, declaration, and amendments filed 5 March 2007 and 20 April 2007 have been entered into the record. Claims 1 – 16, 20, and 23 – 57 are canceled; claims 17 – 19, 21 – 22, and 58 – 62 are pending.

Election/Restrictions

2. Claim 22 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 21 June 2006.

3. This application contains claim 22 drawn to an invention nonelected with traverse in the reply filed on 21 June 2006. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

4. Claims 17 – 19, 21, and 48 – 62 are under examination.

Withdrawn Rejections and Objections

5. The following rejections set forth in the previous office action are withdrawn:

A. The rejection under 35 USC 112, first paragraph, for lack of enablement commensurate in scope with the claims is withdrawn in light of the amendments. The claims are now limited to administration of conjugates comprising megalin-binding RAP fragments defined by both their structure and their function, whereas previously they were defined by function alone. The examiner concedes it would not require undue experimentation to make and use the conjugates to be administered in the claimed methods. Additionally the declaration under 37 CFR 1.132 filed 5 March 2007 is sufficient to overcome the rejection of claims 17 – 19, 21, and 58 – 62 based upon lack of enablement commensurate in scope with the claims. The declaration provides evidence that amino acids 201-319 of SEQ ID NO:1 bind to megalin.

B. The rejection under 35 USC 112, first paragraph for lack of adequate written description is withdrawn in light of the amendments. The claims are now limited to administration of conjugates comprising megalin-binding RAP fragments defined by both their structure and their function, whereas previously they were defined by function alone. The examiner concedes the claims are adequately described by the specification.

C. The rejections under 35 USC 112, second paragraph are withdrawn in light of the amendments. Claim 18 now requires the step of administering, which the examiner had considered essential. Claim 21 now depends from claim 19, so the scope of claim 21 is clear.

D. The rejection of claim 18 under 35 USC 102 over Czekay is withdrawn in light of the amendments. The claim now requires administration of a conjugate to an animal, whereas Czekay teaches administration of the conjugate to cells.

E. The rejection of claims 17 – 19 and 21 under 35 USC 102 as anticipated by Zlokovic is withdrawn in light of the amendments. The claims now require that the conjugate comprise a sequence at least 80% identical to certain RAP residues; the reference by Zlokovic teaches administration of conjugates comprising ApoJ protein, not RAP.

F. The rejections under 35 USC 103 as obvious over Zlokovic are withdrawn in light of the amendments. As set forth above, the reference by Zlokovic does not anticipate the independent claims and does not serve as a reference in a rejection under 35 USC 103.

Maintained Rejections and Objections

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 17 – 19, 21, and 58 – 59 stand rejected under 35 U.S.C. 102(e) as being anticipated by Beliveau (US Patent Application Publication 2003/0129186, published 10 July 2003, filed 25 July 2002, claiming benefit of a provisional application filed 25 July 2001).

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the

inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

This rejection stands for the reasons previously made of record. Briefly, Beliveau teaches conjugates comprising "a peptide ligand of the LRP1 or LRP1B receptor" (see p. 3 paragraph [0026]), and teaches that RAP is such a ligand (see p. 13, Table 3), and also teaches that RAP is a megalin-binding moiety (see Figure 17C). Beliveau also teaches administering the conjugates to animals (see for example p. 3 paragraph [0028]). While Beliveau does not explicitly identify the sequence of RAP, it is reasonable that the sequence from Beliveau comprises a sequence at least 80% identical to residues 221 – 323 of SEQ ID NO:1 (the sequence depicted in Figure 15), as the instant specification identifies this sequence as human RAP and the '186 publication clearly is on point to treatment of humans (see paragraph [0210] for example). As the instant claims are drawn to administering conjugates comprising agents and RAP proteins which comprise a sequence at least 80% identical to residues 221 – 323, the claims read on administering conjugates between agents and full-length RAP. Thus the reference by Beliveau anticipates claims 17 – 19; note that Beliveau defines RAP as a megalin-binding protein (see Table 3).

Claims 21, 58, and 59 are rejected as Beliveau teaches treatment of Huntington's disease with any of the compounds disclosed of his invention (see p. 12, paragraph [0129]), and particularly mentions that the compositions of the invention should be formulated for administration to humans (see for example p. 19, paragraphs [0197] – [0198]).

Applicant argues, on p. 6 of the remarks, that the reference by Beliveau does not teach all elements of the claims. The examiner disagrees. As set forth above, the claims read on administration of full-length RAP conjugated to agents (note use of the open claim language "... RAP fragment that comprises an amino acid sequence at least 80% identical to amino acids 221 – 323 of RAP").

7. Claims 17 – 19, 21, and 58 – 59 stand rejected under 35 U.S.C. 102(a) as being anticipated by Beliveau (WO 03/009815, published 6 February 2003).

The Beliveau '815 publication is identical to the '186 publication above; it appears to differ only in the numbering of the pages. Both publications resulted from applications filed on the same day and claim benefit of the same U.S. Provisional Application. The reasons why the

disclosure anticipates the invention of claims 17 – 19, 21, and 58 – 59 are set forth in the previous rejection.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 17 – 19, 21, and 58 – 62 stand rejected under 35 U.S.C. 103(a) as being obvious over Beliveau (U.S. Patent Application 2003/0129186) in view of Perez-Navarro (2000. Journal of Neurochemistry 75:2190-2199), or in the alternative over Beliveau (WO 03/009815), in view of Perez-Navarro.

The applied reference Beliveau (U.S. Patent Application 2003/0129186) has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This

rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2). Note that these conditions apply only to the reference by Beliveau (US Patent Application Publication 2003/0129186), and not to WO 03/009815, which qualifies as prior art under 102(a).

This rejection stands for the reasons of record. Briefly, both references by Beliveau teach administration of conjugates between RAP and therapeutic agents for treatment of disease, including Huntington's disease; the instant claims read on methods of administering full-length RAP conjugated to therapeutic agents. Beliveau ('186 publication) teaches that growth factors can be used in the conjugates (see p. 3 paragraph [0026]). However Beliveau does not teach using BDNF in the conjugate.

Perez-Navarro teaches that BDNF is neuroprotective when administered to rats in an art-accepted model of Huntington's disease. Thus the reference is on point to claims 21 and 59, which encompass Huntington's disease, and claims 60 – 62, which encompass BDNF. Specifically the Perez-Navarro reference teaches that grafting cells which secrete BDNF into the striatum protects against toxicity of several types of neurons studied (see pp. 2195 – 2197) in art-accepted models of Huntington's disease. Furthermore, the authors contemplate that neurotrophins, including BDNF, should be used for treatment of neurological disorders (see p. 2198, final paragraph).

It would have been obvious to one of ordinary skill in the art to modify the teachings of Beliveau (either the '186 publication or '815 publication) to use BDNF as the active agent, as taught by Perez-Navarro. The motivation to do so would be to treat Huntington's disease. Beliveau teaches that the conjugates can be used to transport active agents across the BBB, and that Huntington's disease is one of the conditions that can be ameliorated by administering the conjugates.

Applicant argues, on p. 7 of the remarks, that the references by Beliveau and Perez-Navarro fail to teach all elements of the claimed invention. First, it is noted that points 1) and 2) in the last full paragraph of p. 7 are not claimed features of the invention but rather are potential mechanisms which explain experimental results in the disclosure. Whether or not the references teach these particular features is not germane to the question of obviousness, as these are limitations which are not claimed. With respect to point 3), whether the references teach administration of agents conjugated to fragments, it is noted that the claims read on

administration of agents conjugated to a protein that comprises residues 221 – 323 of SEQ ID NO:1. That is, the claims read on administration of full-length RAP conjugated to an agent, which is taught by both Beliveau references. Thus the rejection under 35 USC § 103 stands for the reasons of record.

Double Patenting

9. Claims 17 – 19, 21, and 58 – 62 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 3 – 6 and 14 of copending Application No. 11/202566. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are generic with respect to the structure of the megalin-binding moiety, while the claims in the '566 application are specific in that they require at least 80% sequence identity to RAP. Thus the claims in the '566 application would anticipate the instant claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

This rejection stands for the reasons of record. Applicant did not traverse the rejection.

Inventorship

10. Claims 17 – 19, 21, and 58 – 62 are directed to an invention not patentably distinct from claims 3 – 6 and 14 of commonly assigned 11/202566 as set forth in the double-patenting rejection above. The inventive entities are not identical between the '566 application and the instant application, and there is no evidence of record that the two applications are currently commonly assigned.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned 11/202566, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

This rejection stands for the reasons of record. Applicant did not traverse the rejection.

Rejections and Objections Necessitated by Amendment

Claim Objections

11. Claims 17 – 19 are objected to because of the following informalities:

The claims refer to amino acid sequences but do not recite SEQ ID NOs. 37 CFR 1.821(d) requires that sequences in patent claims be referred to by SEQ ID NO. It is noted that the specification discloses that the protein depicted in Figure 15 is that of SEQ ID NO:1 (see p. 18 line 16).

Appropriate correction is required.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 17 – 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Lenting (WO 00/28021, published 18 May 2000), as evidenced by Lenting (U.S. Patent 6,919,311).

The Lenting '311 patent issued as a national stage entry of PCT/AT99/00272, which served as the basis of the Lenting '021 publication. Since 35 USC § 372(b)(3) requires that the application be submitted in English upon entry to the national stage, the '311 patent is a proper translation of the earlier-published '021 document. While the disclosures are identical, the text below refers to column and line numbers of the '311 patent, which is in English.

Lenting teaches a fusion protein, which is reasonably a "conjugate" as recited in claims 17 and 18, which comprises RAP and GST (glutathione-S-transferase), and administration of this conjugate to mice, which are animals. See Lenting '311, column 14 lines 35 – 50. While the reference by Lenting does not teach the actual sequence of RAP, it is reasonable that the

fusion protein comprises residues 221 – 323 as it is the 39kDa form of RAP. As Lenting teaches administration of the conjugate to animals, which is the only active step recited in claims 17 and 18, the effects recited in the preambles (deliver agent into CNS and increasing transcytosis as recited in claims 17 and 18 respectively) will necessarily occur.

Allowable Subject Matter

13. The prior art does not teach or suggest administration of conjugates consisting of residues 221 – 323 of SEQ ID NO:1 and a therapeutic agent.

Conclusion

14. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

A. Saenko et al. (WO 00/71714, published 30 November 2000). The reference teaches administration of RAP protein (see p. 20 lines 8 – 12) as well as specific fragments, including those 100 residues long (p. 29 lines 6 – 8) and fragments including residues 203 – 319 (p. 30 lines 3 – 7). Note RAP is Saenko's SEQ ID NO:4 and has the sequence of GenBank accession number P30533 (see p. 12 lines 15 – 25), which is the same as applicant's SEQ ID NO:1. Saenko also teaches fusion proteins comprising RAP (p. 14 lines 19 – 22). However Saenko does not explicitly teach administration of conjugates comprising RAP.

B. Mintz et al. U.S. Patent Application Publication 2007/0083334, published 12 April 2007, application filed 31 May 2006, claiming benefit of earlier-filed application 10/242799 filed 13 September 2002. Mintz teaches SEQ ID NOs:775313 and 775320, each of which comprise a sequence 100% identical to residues 221-323 from applicant's SEQ ID NO:1. Mintz also teaches SEQ ID NO:1008505, which comprises a sequence 87% identical to residues 221-323 from applicant's SEQ ID NO:1. Amino acid sequence alignments are attached. However the reference does not teach administration of conjugates comprising these proteins.

C. Obermoeller et al. 1997. Journal of Biological Chemistry 272:10761 – 10768, cited on IDS filed 5 March 2007. The reference teaches a conjugate comprising GST and residues 191-323 of RAP (see Figure 2A for example) and teaches contacting said conjugate to cells but does not teach administration to an animal or conjugates between residues 221-323 of RAP and an agent.

15. No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel Kolker whose telephone number is (571) 272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Daniel E. Kolker, Ph.D.
June 26, 2007

ROBERT C. HAYES, PH.D.
PRIMARY EXAMINER